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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,673	05/08/2001	Jonathan M.J. Derry	3198	3258

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EXAMINER
SMITH, CAROLYN L

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/15/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,673	DERRY ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1 and 3-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' election of Group II (claim 2) and Specie A (method for identifying compounds that inhibit binding of NEMO and CYLD wherein the compounds are antibodies), and withdrawal of claims 1 and 3-24 in Paper No. 9, filed 11/4/02, are acknowledged. Upon reconsideration of the application, Examiner has withdrawn the sequence election requirement.

Applicants' submission that the election between two species is not an unreasonable number of species from which to require a specie election is found unpersuasive. The Examiner maintains that examining both species together would be an undue search burden as they are distinct chemical entities featuring different critical features, as stated in the previous office action.

The requirements are still deemed proper and are therefore made FINAL.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to screening assays for agonists or antagonists of CD40 signaling, whereas in contrast the elected claim is specifically directed to a method for identifying compounds that inhibit the binding activity of NEMO and CYLD.

Claim 2 is herein under examination.

Specification

The disclosure is objected to because of the following informalities: "amin acid" is misspelled on page 5, line 25; the misuse of a period on page 10, line 27; and "CLD" is misspelled on page 13, line 16. Appropriate correction of these and any other mistakes is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, such as on page 16, line 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

PATENTABLE UTILITY GUIDELINES

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

Claims Rejected Under 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 2 is rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility.

Claim 2 pertains to a method for identifying compounds that inhibit binding between NEMO and CYLD. The method identifies compounds but it falls short of a readily available utility of allowing "regulation of specific pathways in an inflammatory response" by affecting inhibitors with NEMO (page 2, lines 24-27), particularly with "other molecules in the CD40 signaling cascade (i.e. CYLD)" (page 6, lines 22-24). The specification states this inhibition of interactions "*will be* useful in downregulating or controlling deleterious effects" and "conditions that *are thought to be* mediated by CD40 signaling include atherosclerosis, arthritis, multiple sclerosis (MS), systemic lupus erythematosous (SLE), thrombosis, graft versus host disease and/or graft rejection" (page 6, lines 22-28), but never connects any specifically identified compounds to any particular or available utility. The above-mentioned list of desirable utility for the compounds identified in the method falls short of a readily available utility.

Furthermore, the claimed method is not supported by a substantial utility because no substantial utility has been established for the claimed method. For example, Applicants state that NEMO can bind with various molecules in the CD40 signaling cascade, such as CYLD (page 6, lines 23-24), and that CYLD is a "putative tumor suppressor gene associated with familial cylindromatosis" (page 2, lines 16-17). The apparent need for further research to determine if inhibiting the binding of NEMO and CYLD does, in fact, play a role in the possible

utilities as mentioned in the previous paragraph indicates the claimed method is not disclosed as to a current available or substantial utility. Also, relying on putative functions of genes does not define a "real world" context of use. Similarly, the other listed utilities and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to many such compounds.

Applicants should explicitly identify a specific, substantial, and credible utility for the claimed invention and establish a probative relation between any evidence of record and the originally disclosed properties of the claimed invention. Due to a lack of either an art recognized or alleged well established utility, the instant invention has been rejected due to also lacking the required combination of a specific, substantial, and credible utility. Although it may be credible that one or more compound(s) affect and/or regulate pathway(s) in an inflammatory response, the lack of a specific and substantial utility, as explained above, sufficiently supports this rejection.

It is noted that applicants discuss the idea of using sequences which are known in the prior art and which have a stated sequence similarity to SEQ ID NOs: 2 and 4. Absent factual evidence, one skilled in the art would have reason to doubt that sequence similarity alone would reasonably support the assertion that the biological activity of the claimed subject matter would be the same as that of the similar sequence. Furthermore, it is unclear whether the similar sequence identified in the prior art has actually been tested for the biological activity or whether this also is an asserted biological activity based upon sequence similarity to yet a different sequence. Note that it would have been well known in the art that sequence similarity does not reliably correlate to structural similarity and that structural similarity does not reliably result in similar or identical biological activities. For example, it would have been well known that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. In the absence of factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely

unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. Several publications document the unpredictability of the relationship between sequence, structure, and function, although it is acknowledged that certain specific sequences have been found to be conserved in biomolecules having related function following a significant amount of further research. See Lopez et al. (Molecular Biology, 32:881-891,1999); Attwood (Science, 290:471-473, 2000); Gerhold et al. (BioEssays, 18(12):973-981, 1996); Wells et al. (Journal of Leukocyte Biology, 61(5):545-550, 1997); and Russell et al. (Journal of Molecular Biology, 244:332-350, 1994). However, this level of factual evidence is absent here.

Claim 2 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, albeit generally credible or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Claims Rejected Under 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF ENABLEMENT

Claim 2 is rejected under 35 U.S.C. §112, first paragraph. While being enabling (subject to the above lack of enablement rejection) for identifying compounds that inhibit the binding activity between full length polypeptides of NEMO and CYLD, the specification does not reasonably provide enablement for identifying compounds that inhibit the binding activity of

NEMO and CYLD polypeptides via fragments and variants. The claim is broader than the enablement provided by the disclosure with regard to the large number of possible fragments and variants that could be utilized which may or may not still exhibit NEMO and CYLD characteristics. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the instant claim.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claim 2 is directed to a method for identifying compounds that inhibit the binding activity between NEMO and CYLD polypeptides, fragments, and variants. However, claim 2 does not adequately limit the fragments and variants of NEMO and CYLD that still contain the NEMO and CYLD characteristics and properties including their binding activities.

It would require undue experimentation for a person having ordinary skill in the art to practice the claimed invention due to the unpredictability of knowing what degree of variance or

what fragment involved would still allow the NEMO and CYLD polypeptides to be biologically active. The NEMO and CYLD components used directly affect the outcome of the claimed method, and Applicants have not shown how independent variation of one or more components in the scheme would affect the outcome of the claimed method. Due to the above-mentioned unpredictability, a skilled artisan would not be able to practice the claimed invention without undue experimentation.

LACK OF WRITTEN DESCRIPTION

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification discloses SEQ ID NOs: 2 and 4 which corresponds to NEMO and CYLD polypeptides, respectively. SEQ ID NOs: 2 and 4 meet the written description provisions of 35 USC 112, first paragraph. However, claim 2 is directed to encompass fragments and variants capable of binding to NEMO and CYLD polypeptides. The only fragment or variant that meets the written description provision of 35 USC 112, first paragraph, is fragment 287-419 of SEQ ID NO: 2. Due to the open claim language of "comprising" as stated on line 4, claim 2 also encompasses other polypeptide sequences that do not meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: XXX, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only SEQ ID NOs: 2 and 4 and fragment 287-419 of SEQ ID NO: 2 but not the full breadth of the claim meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite due to the unclarity of citing an abbreviation, such as NEMO and CYLD on lines 1 and 2 of the claim, respectively. Correction is suggested by amending in of the full name in parentheses.

Claim 2 recites the phrase "compounds that inhibit binding of NEMO and CYLD" on lines 1 and 2 which is vague and indefinite. It is unclear whether the compounds to be identified will inhibit binding between NEMO and CYLD or inhibit binding of NEMO and CYLD to other compounds. Clarification via clearer claim wording is required.

Claim 2, line 4, recites the phrase "comprising amino acids 287 through 419 [of] SEQ ID NO: 2" which is vague and indefinite. Due to the open claim language, it is unclear whether the amino acid sequence mentioned is referring to the entire portion of residues 287 to 419 or just a section within it. Appropriate clarification of the metes and bounds of the claim via clearer wording is required.

Claim 2, lines 5, 8, and 9, recites the phrase "according to" which is vague and indefinite. The claim does not adequately define to what extent the "according to" must be followed. Appropriate clarification of the metes and bounds of the claim via clearer wording is required.

Claim 2 recites the phrase "capable of binding" on lines 5, 9, and 11 which is vague and indefinite. It is unclear what the phrase means as far as the amount of binding required and the criteria including their necessary extent to determine the *capability* in such binding. For

example, must the binding affect an inflammatory response? Clarification of the metes and bounds of the instant claim with clearer claim wording is required.

Claim 2 recites the word "variant(s)" on lines 6 and 10 which is vague and indefinite. The claim does not adequately define the phrase which could mean a variant which is 5% different and of the same length as the claimed polypeptides or 20% different and only a fragment of the sequence or any other scenario. Appropriate definition regarding the degree of variation to the claimed polypeptides is required.

Claim 2, line 12, recites the phrase "inhibits the binding activity" which is vague and indefinite. It is unclear to what degree (perhaps percentage) of activity is inhibited, as the amount of activity could range anywhere from 0% to 100%. Clarification of the metes and bounds of the instant claim with clearer claim wording is required.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

December 30, 2002

ARDIN H. MARSCHEL
PRIMARY EXAMINER